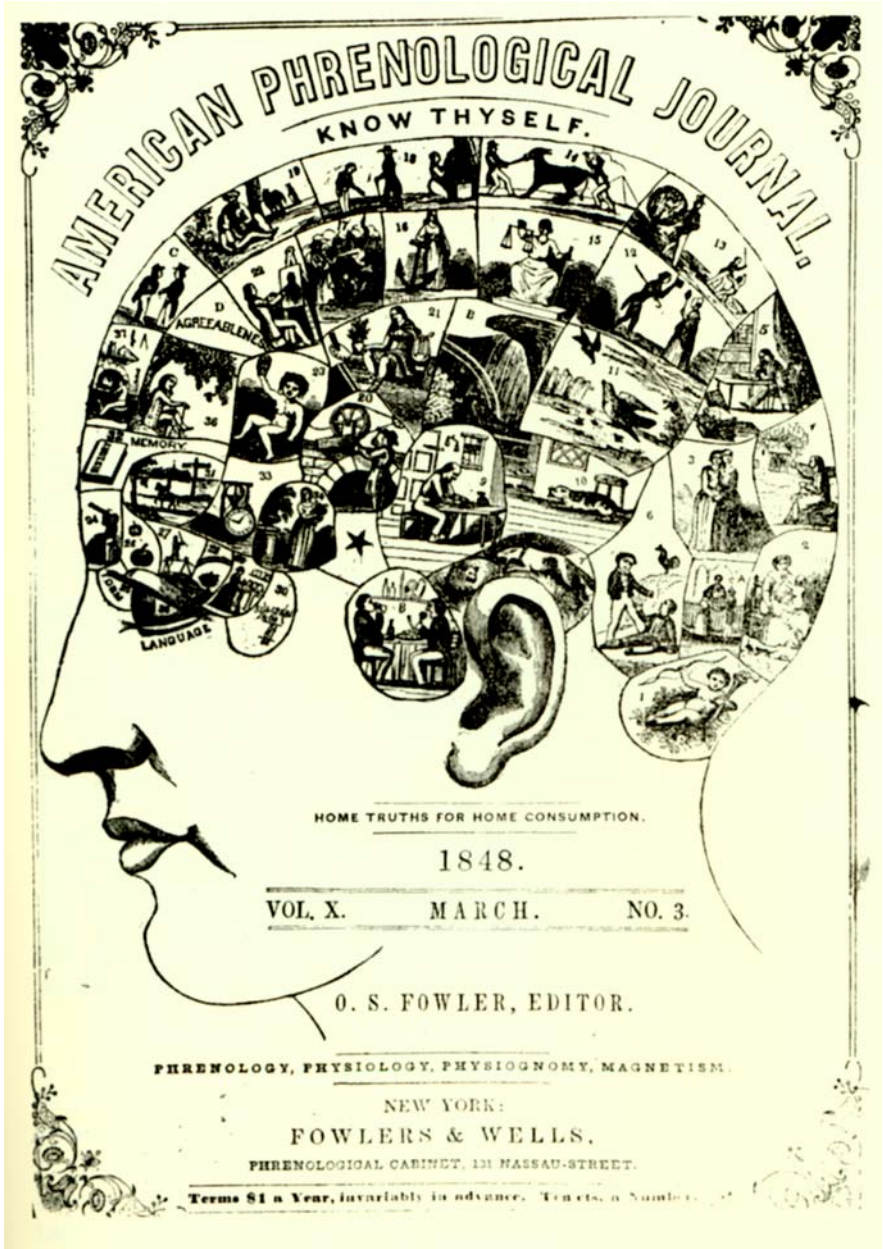
NEUROSCIENTIFIC FOUNDATIONS OF PSYCHIATRY

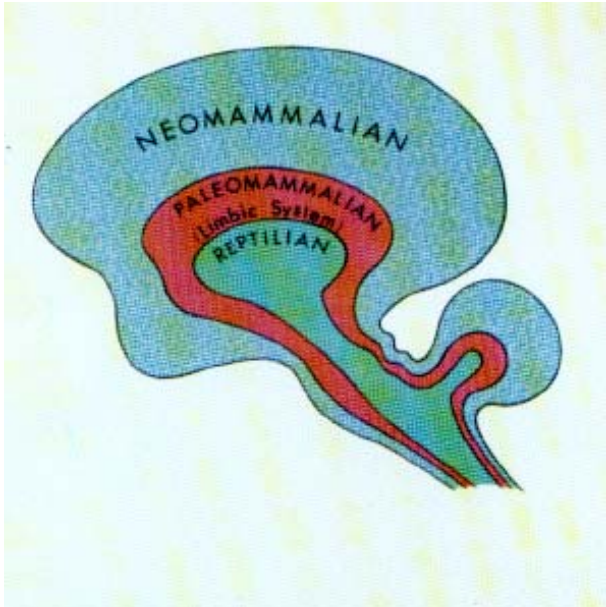
Timothy Lacy, M.D., Lt Col, USAF, MC



“The Big Picture”

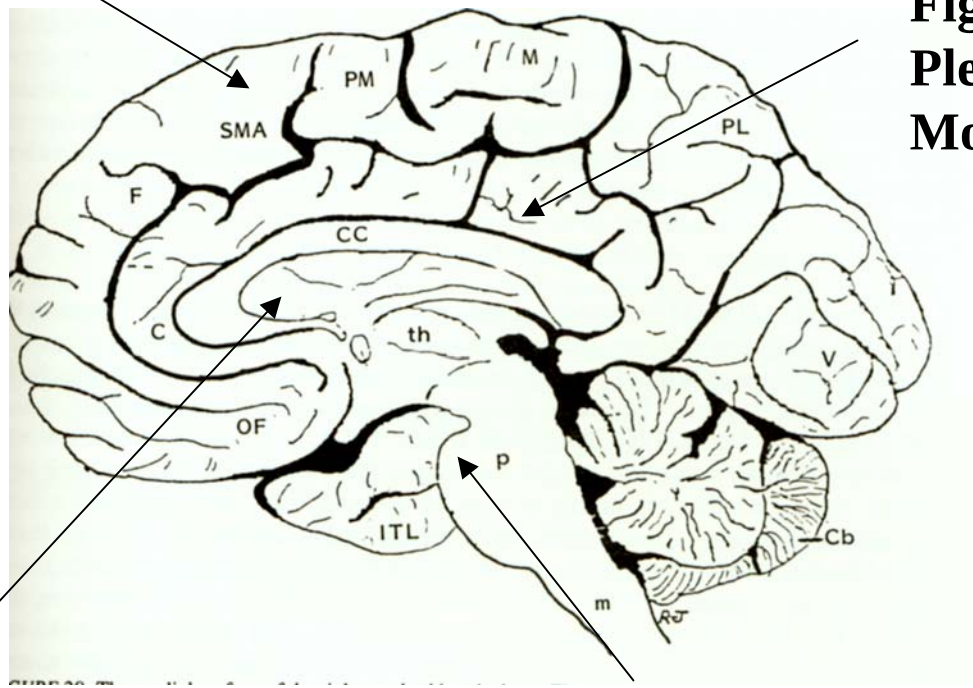
Brain Organization

The Triune Brain



Symbolic
Abstract
Reasoning
Choice
Will
Memory
Sensory Processing

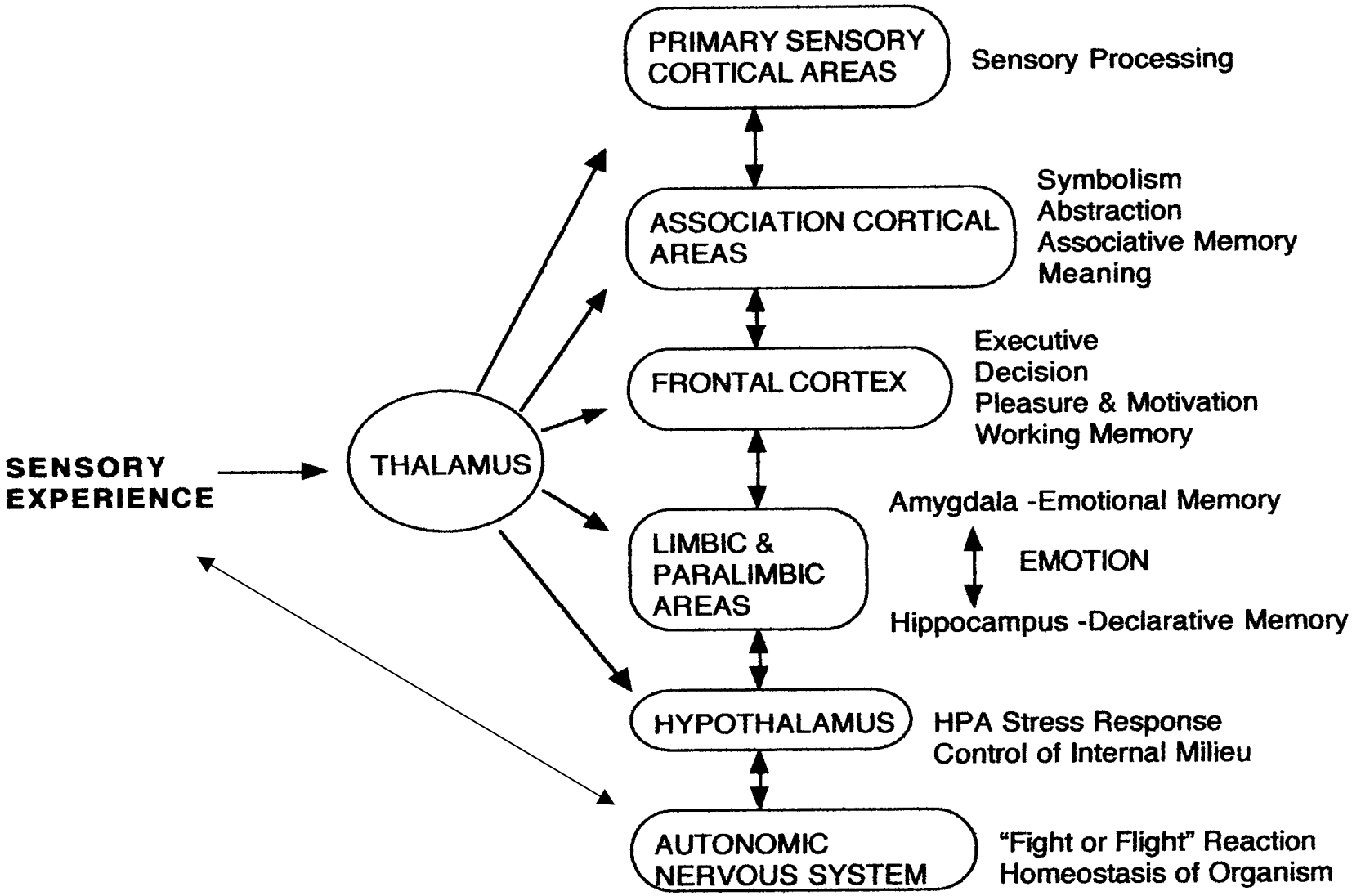
Emotional Experience
Memory Processing
Territorial/Mating
Fight-flight
Pleasure
Motivational Systems



Rituals
Routines
Survival Patterns

Homeostasis
Approach-avoidance/Fight-flight
Stress Response, Hormonal Control
Primitive Routines and Habits
Sets tone for entire CNS
Where most neurotransmitters are made

INTERRELATED BRAIN SYSTEMS



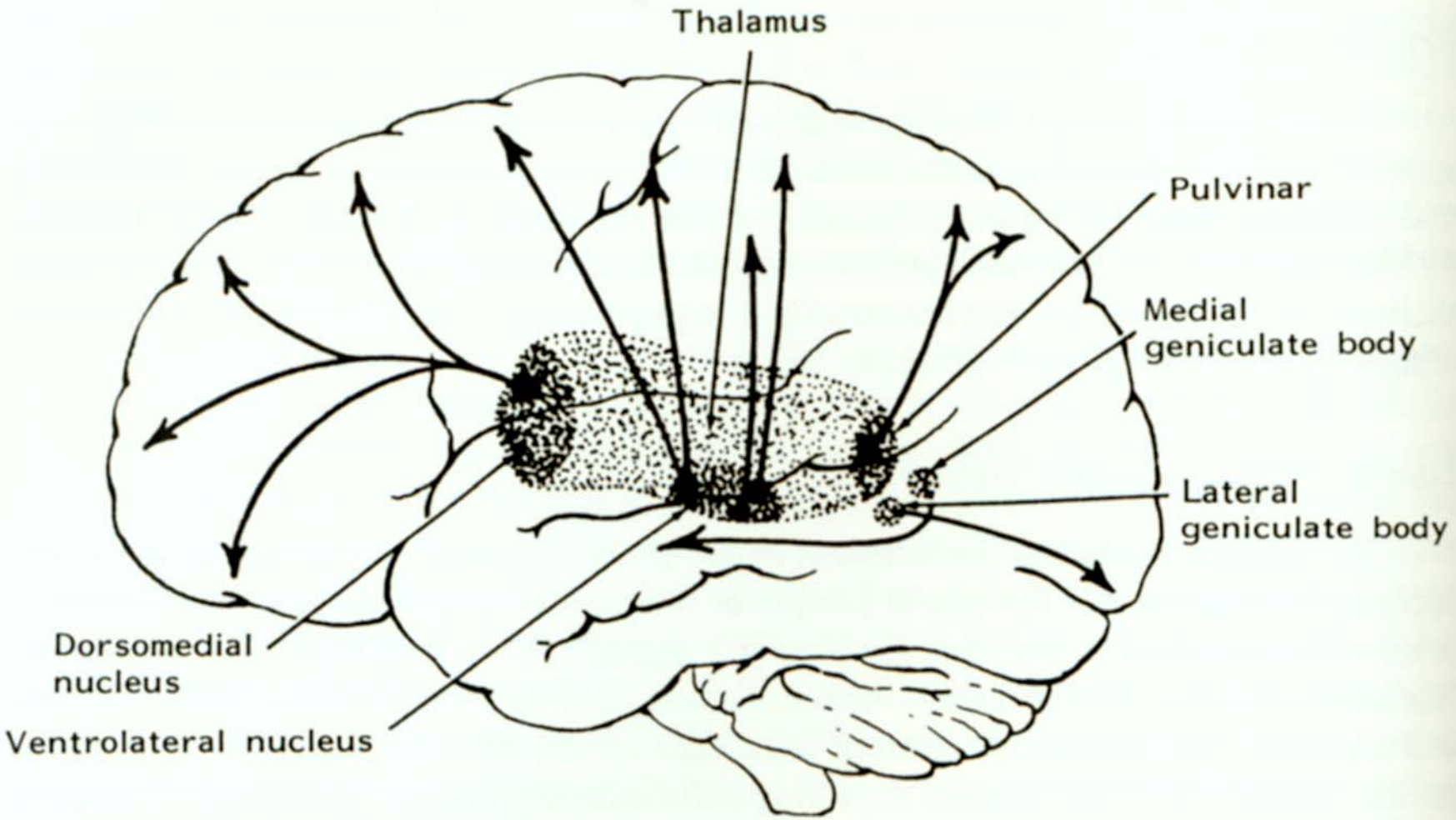
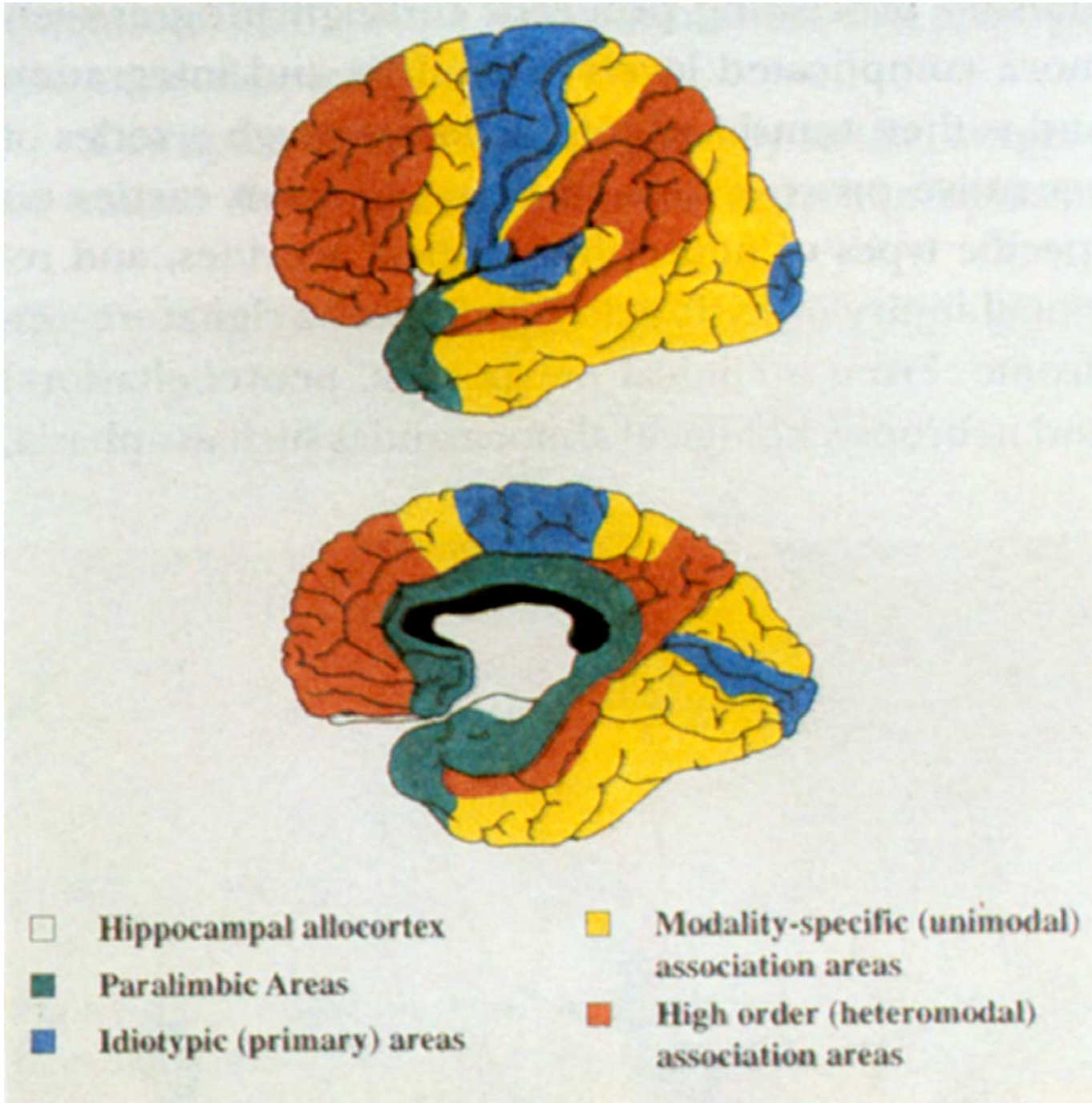


FIGURE 35. Diagram of principle thalamocortical projections. Reproduced, with permission, from *Correlative neuroanatomy,* 20th Ed., by J. DeGroot & J. G. Chusid, copyright Appleton & Lange, E. Norwalk, CT, 1988.


Hippocampal allocortex
Paralimbic Areas
Idiotypic (primary) areas
Modality-specific (unimodal) association areas
High order (heteromodal) association areas

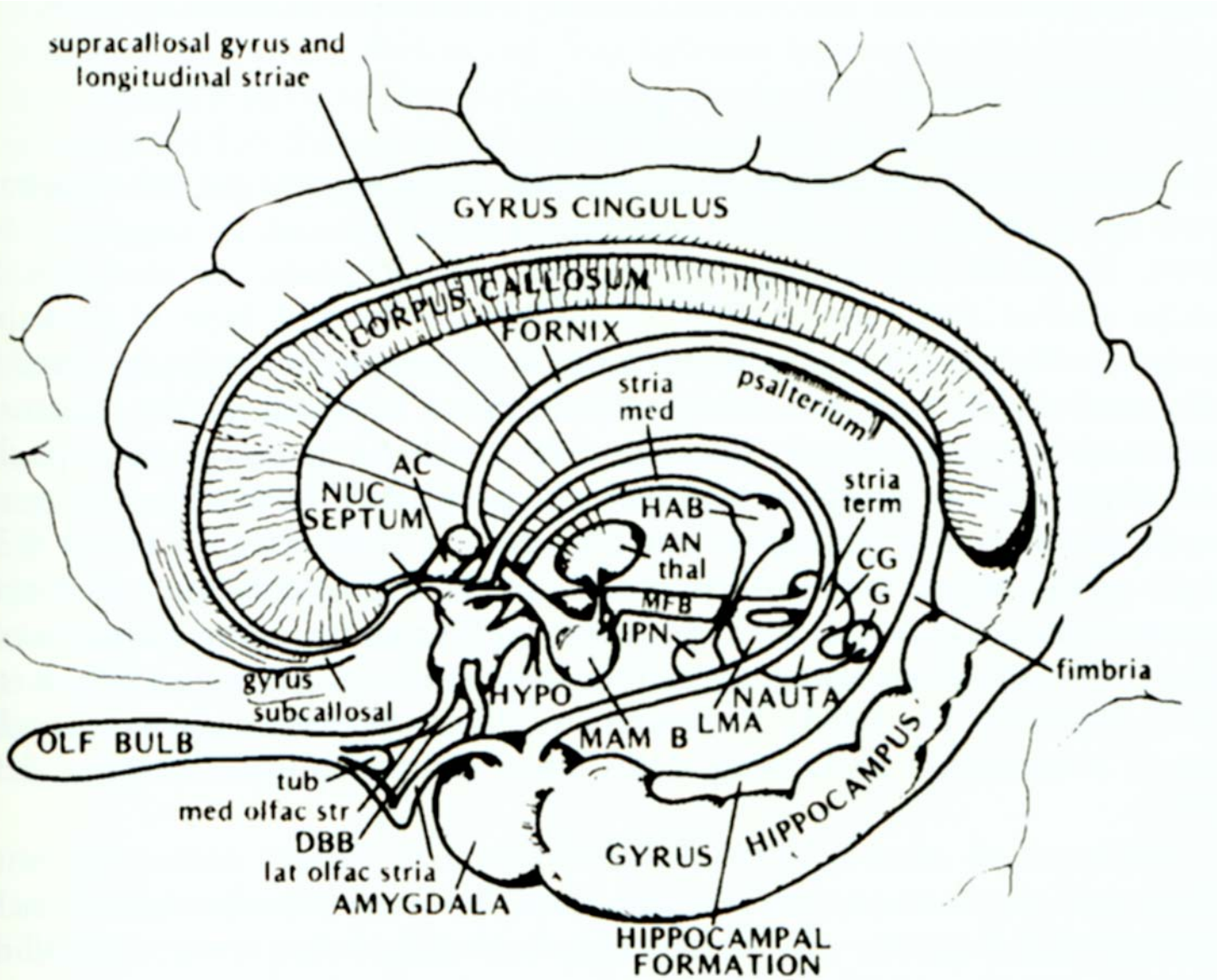
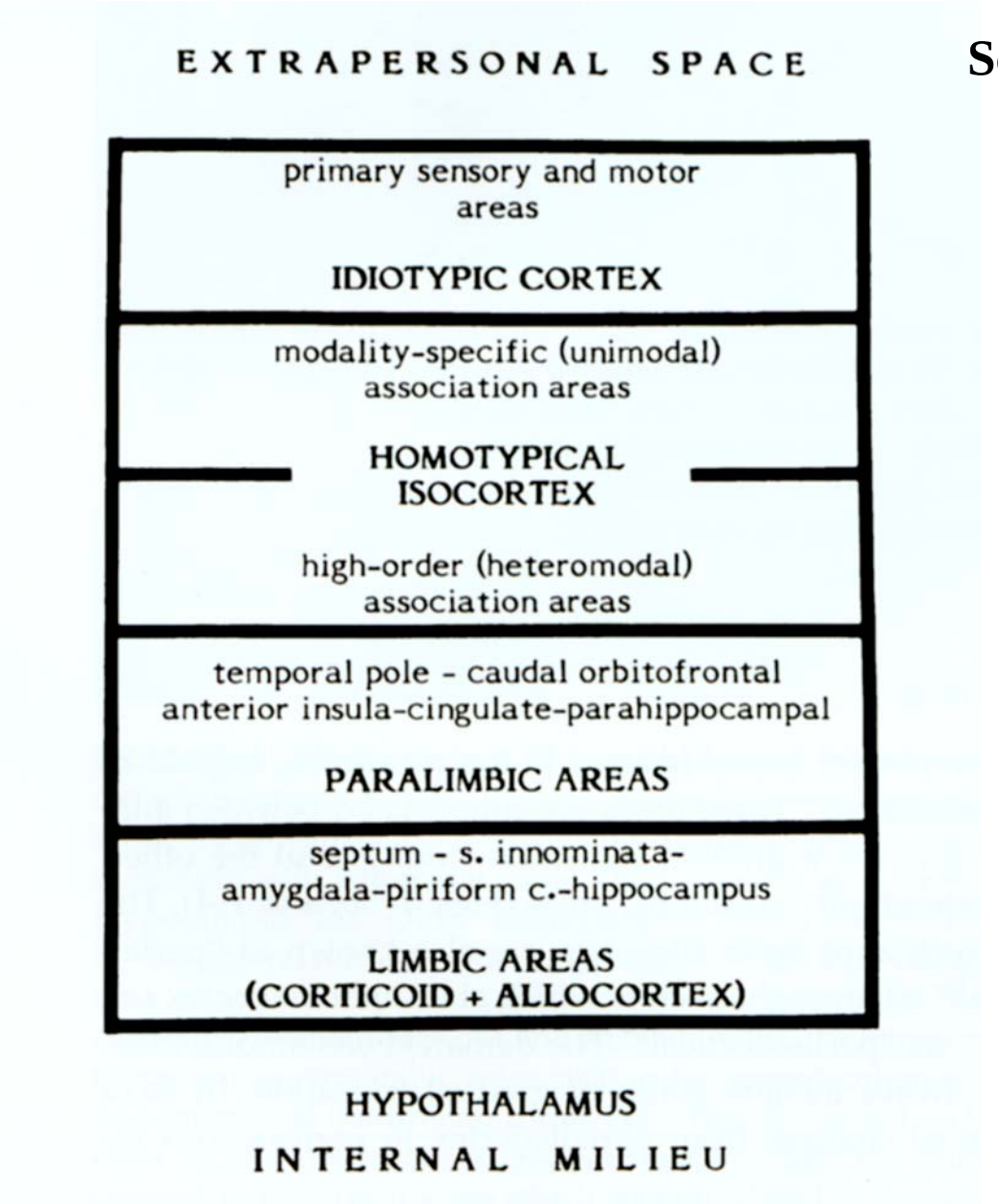


Fig. 9.2. Schematic illustration of the hippocampal–limbic system. Of proved significance for learning are the hippocampal formation, fimbria, fornix and mamillary bodies; these structures represent an inner core of the limbic system. From Heilman et al., 1985a.



Sensory and Motor Function

↕

Symbolic, Abstract
Reasoning, Choice
Will, Memory

↕

Emotional Experience
Memory Formation
Rituals and Routines

↕

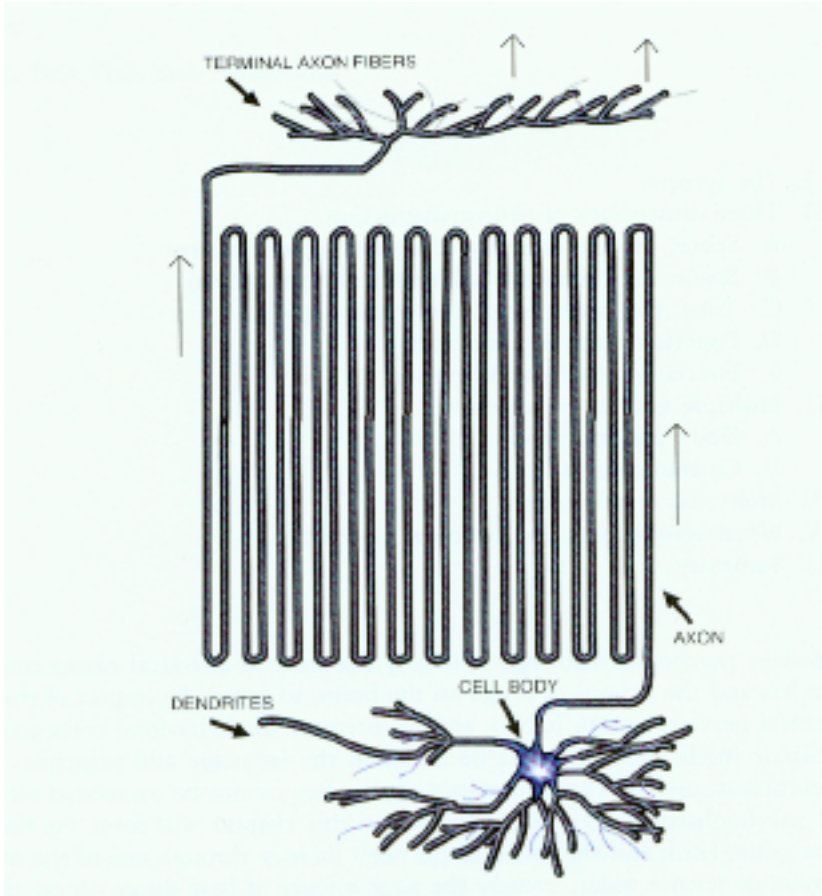
Homeostasis
Approach-avoidance
Stress Response
Hormonal Control
Sets tone for entire CNS

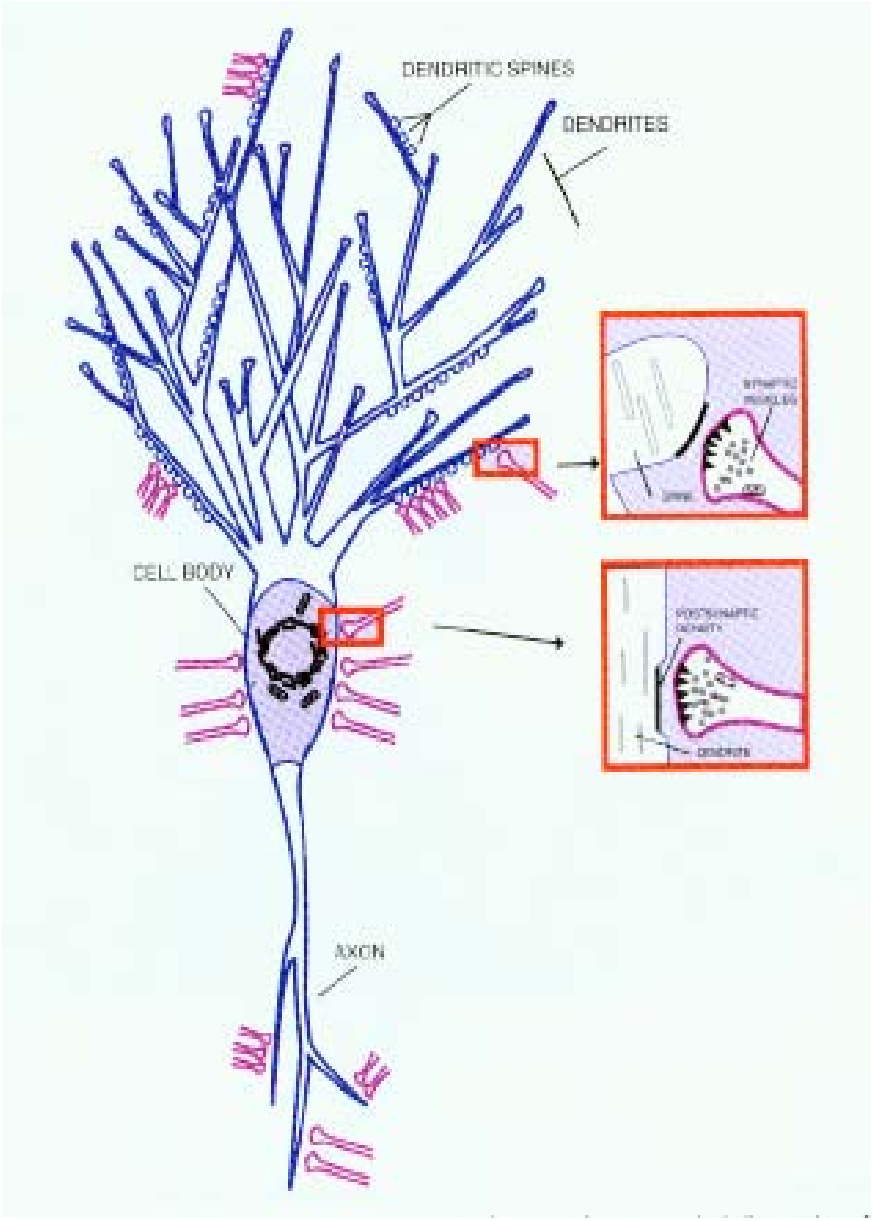
Disturbance in one “part” affects the function of the “whole”

The Details of Brain Function

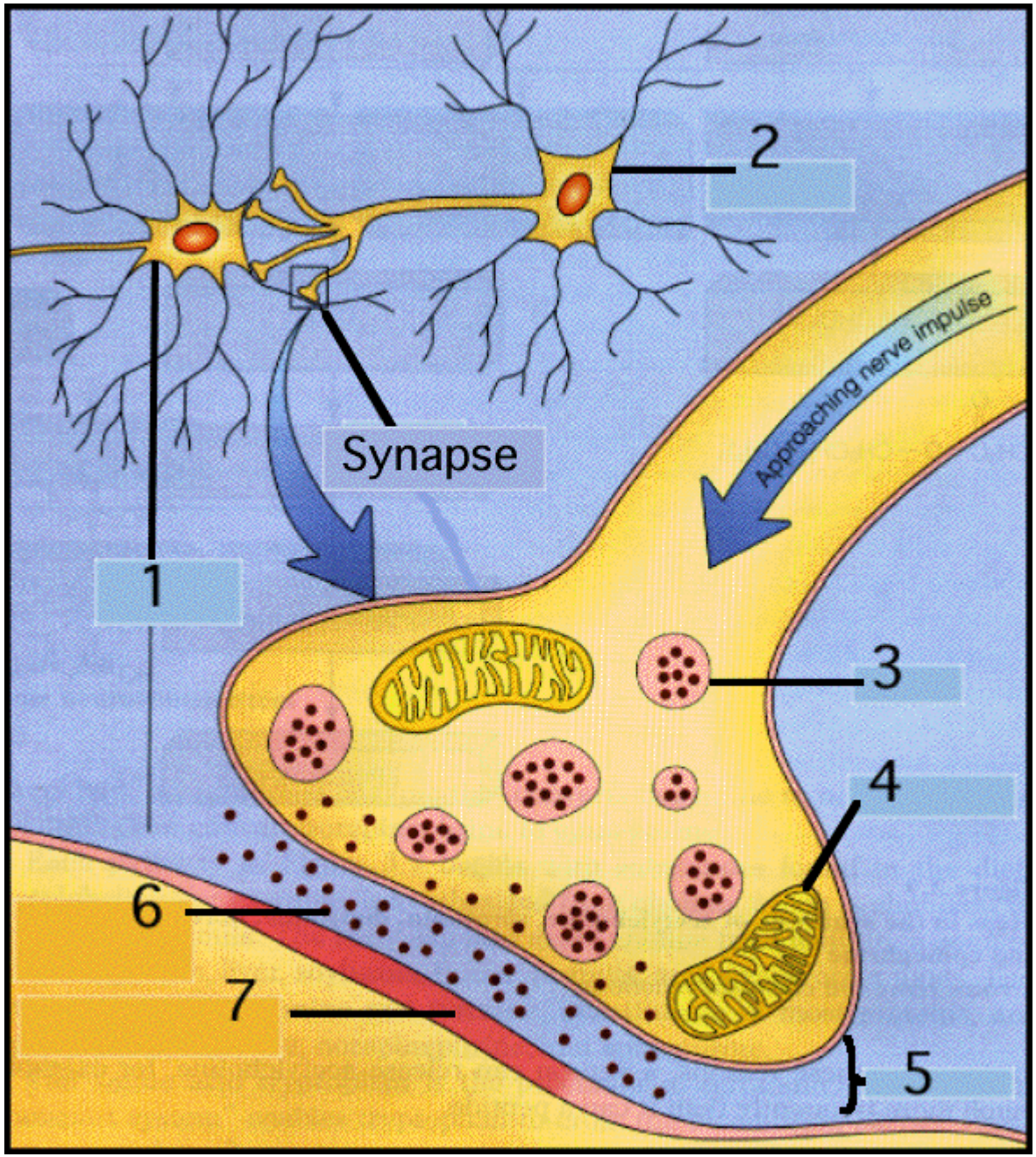
FUNCTIONAL ANATOMY OF A NEURON

- Cell Body (perikaryon)
- Dendrites
- Axon
- Axon Terminal
- Synapse

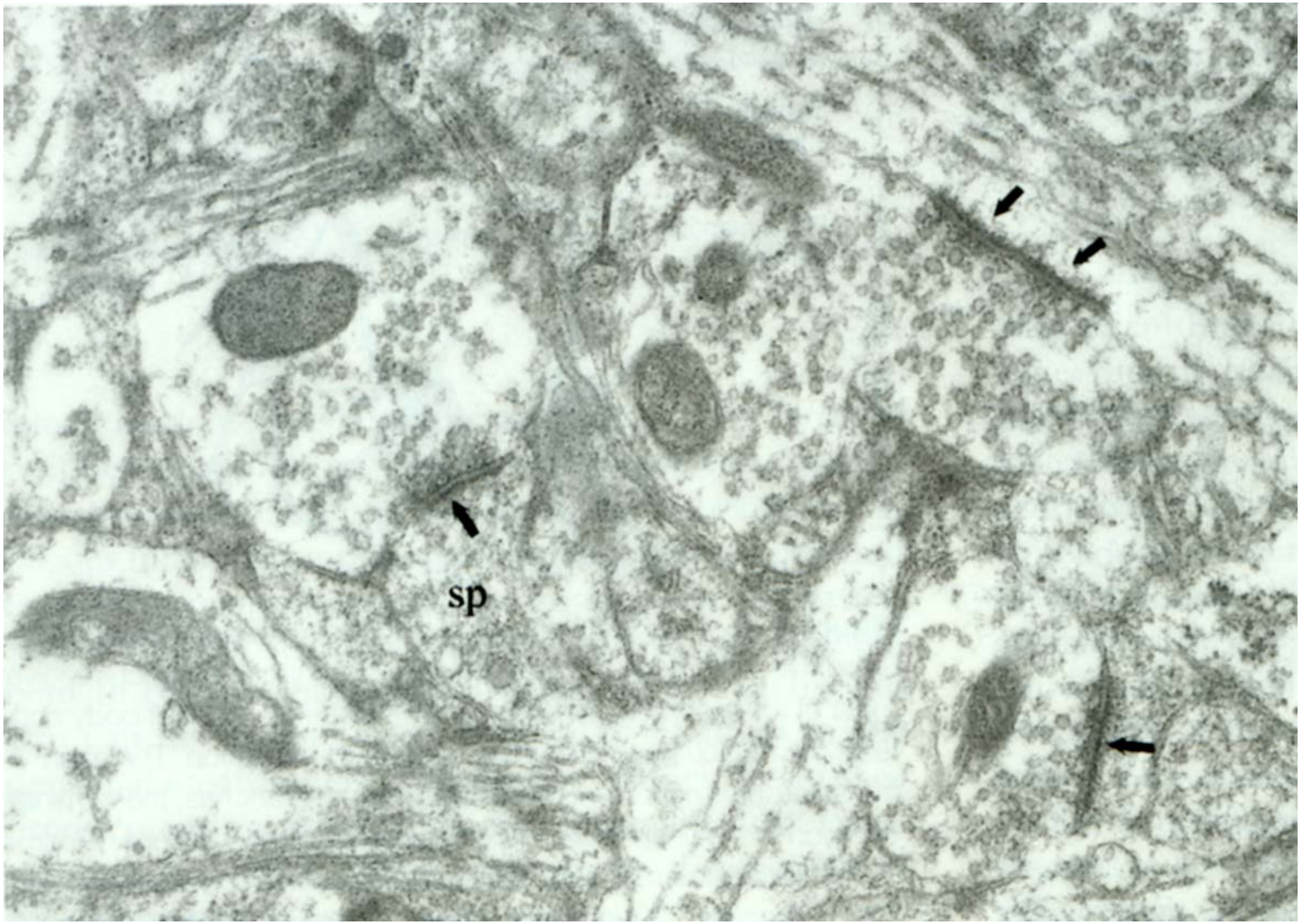




The Neuron


2
Synapse
Approaching nerve impulse
1
3
4
6
7
5

THE SYNAPSE



Electrical conduction

- Ion pumps (Na+/K+) (Ca++)
- Resting membrane potential (-70 mV)
- Action potential (-35 mV)
- Voltage-gated ion channels (Na+, Ca++)

The Action Potential

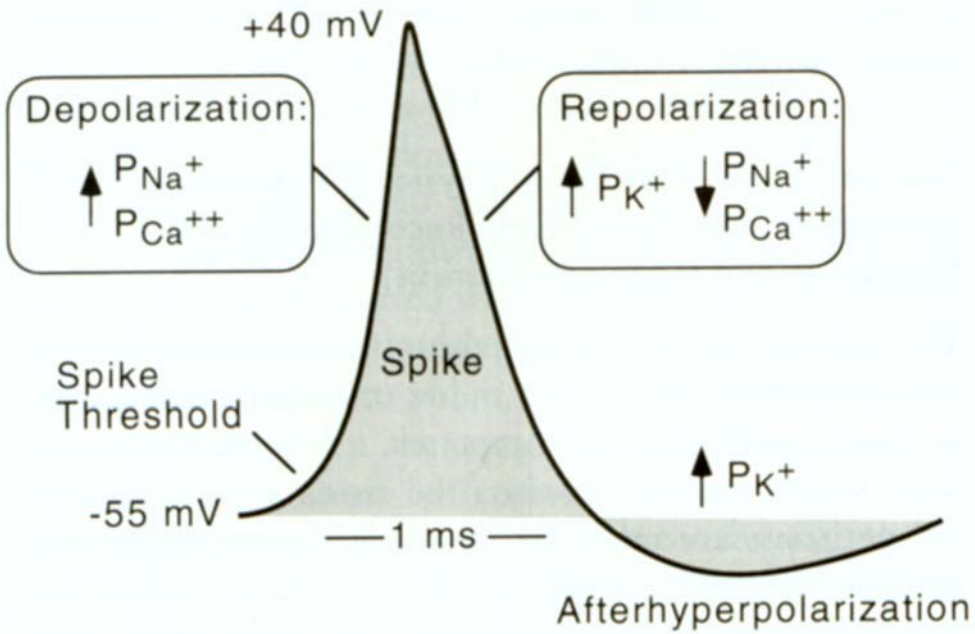


FIG. 3.1 Description of the changes in ionic permeability (P) that result in the upstroke, downstroke, and afterhyperpolarization of action potentials in neurons.

Neurotransmitters

- Criteria
  - contained in a neuron
  - made in the neuron
  - neuron releases it
  - physiologically active on neurons
- Two Classifications (so far)
  - Classical
  - Neuropeptide

NEUROTRANSMITTERS
KEY QUESTIONS

- *Where is it made?*
- *Where does it go?*
- *How is it made and what is the rate limiting step in its production?*
- *How is it metabolized?*
- *Role in the CNS?*
- *Clinical significance?*

CLASSICAL NEUROTRANSMITTERS

- Norepinehrine
- Serotonin
- Acetylcholine
- Histamine
- Glutamate
- Homocysteine

- Epinephrine
- Dopamine
- GABA
- Aspartate
- Glycine
- Taurine

Neuropeptide Neurotransmitters

too many to list them all

- **Opioid peptides**
  - **Endorphins, enkephalins**
- **Gut-brain peptides**
  - **VIP, CCK, Secretin, Gastrin, Somatostatin**
- **Bradykinin peptides**
  - **Substance P, others**
- **Pituitary peptides**
  - **Oxytocin, Vasopressin, ACTH,**
- **Hypothalamic peptides**
  - **CRF, TRF, GHRF**

Neurotransmitter Production

- Classical neurotransmitters - synthesized in the terminal bouton
- Neuropeptide neurotransmitters - produced in the cell body and transported to the bouton

Production of classical neurotransmitter in the terminal bouton

Pre-synaptic terminal –terminal bouton

Post-synaptic terminal

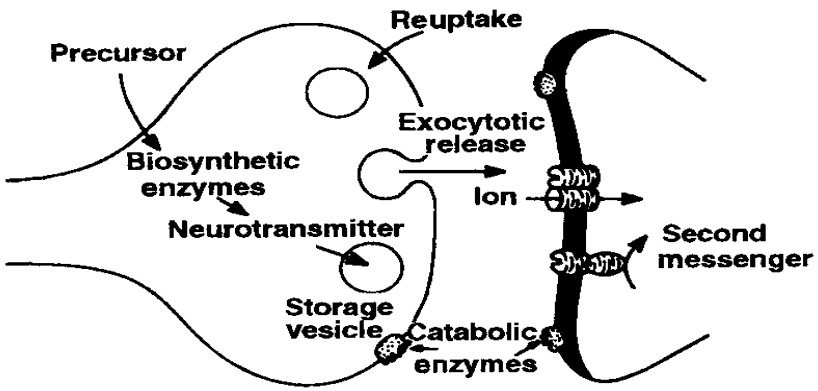


FIGURE 1–3. Schematic representation of the processes involved in the synthesis, synaptic action, and inactivation of classical neurotransmitters.

Neuropeptide neurotransmitters - produced in the cell body and transported to the bouton

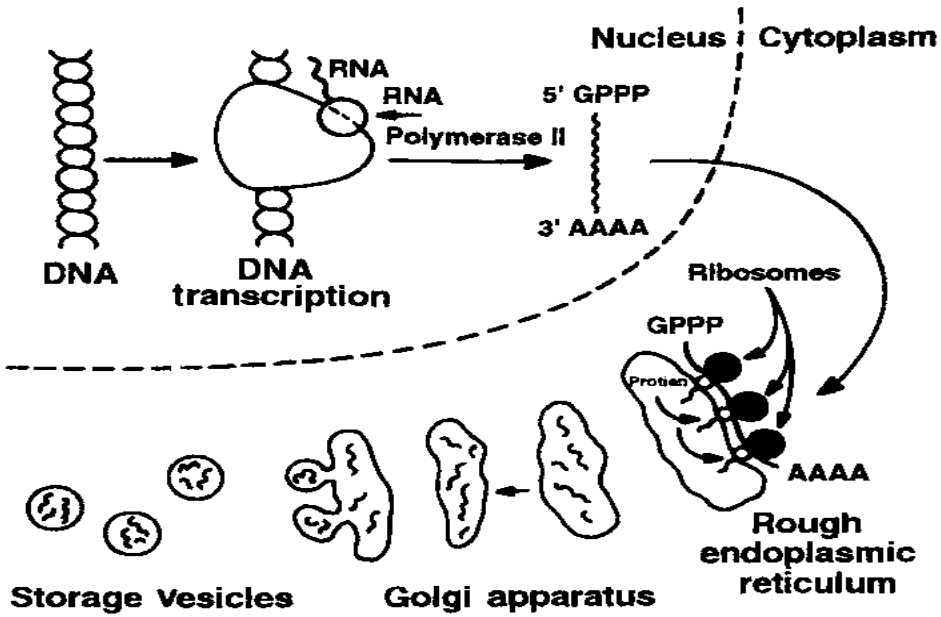


FIGURE 1-4. Sequence of neuropeptide synthesis. Within the nucleus, the gene for the precursor neuropeptide is transcribed into mRNA. The mRNA is transported from the nucleus into the cytoplasm, where it binds to ribosomes. The mRNA is then translated via protein synthesis on the ribosomes in the rough endoplasmic reticulum. Within the Golgi apparatus, the precursor peptide is enzymatically modified to yield the neuropeptide, which is packaged in storage vesicles for axoplasmic transport to the nerve terminal.

Neuropeptide neurotransmitters - precursors modified in the Golgi apparatus

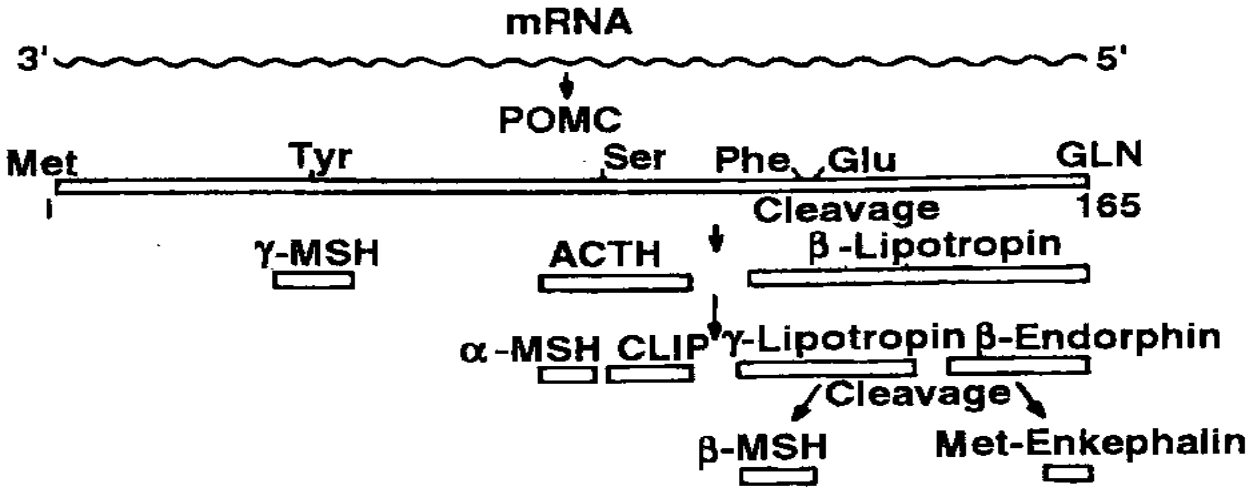
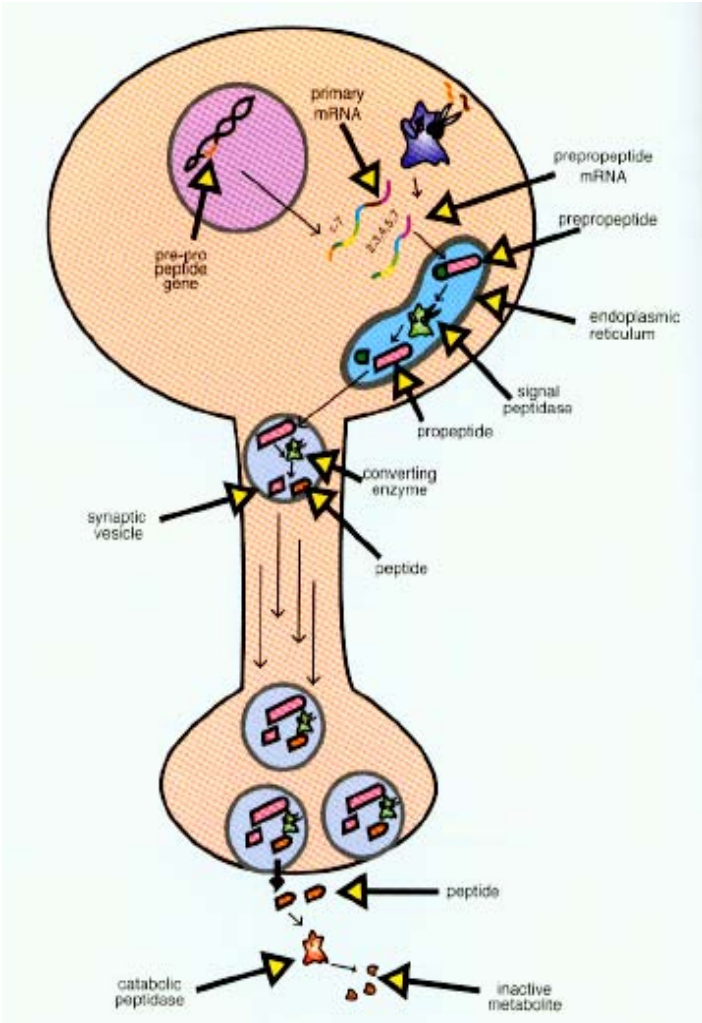


FIGURE 1–5. Processing of proopiomelanocortin (POMC). The precursor protein POMC, which contains 165 amino acids, is enzymatically cleaved to yield the physiologically active peptides indicated. Depending on the cellular localization (anterior pituitary, hypothalamus, midbrain nerve terminals), certain of these neuropeptides are expressed and others are not (see Watson et al. 1985).

Neuropeptide neurotransmitters - produced in the cell body and transported to the bouton



NOREPINEPHRINE

- *Where is it made?*
- LOCUS CERULEUS (projects throughout brain)

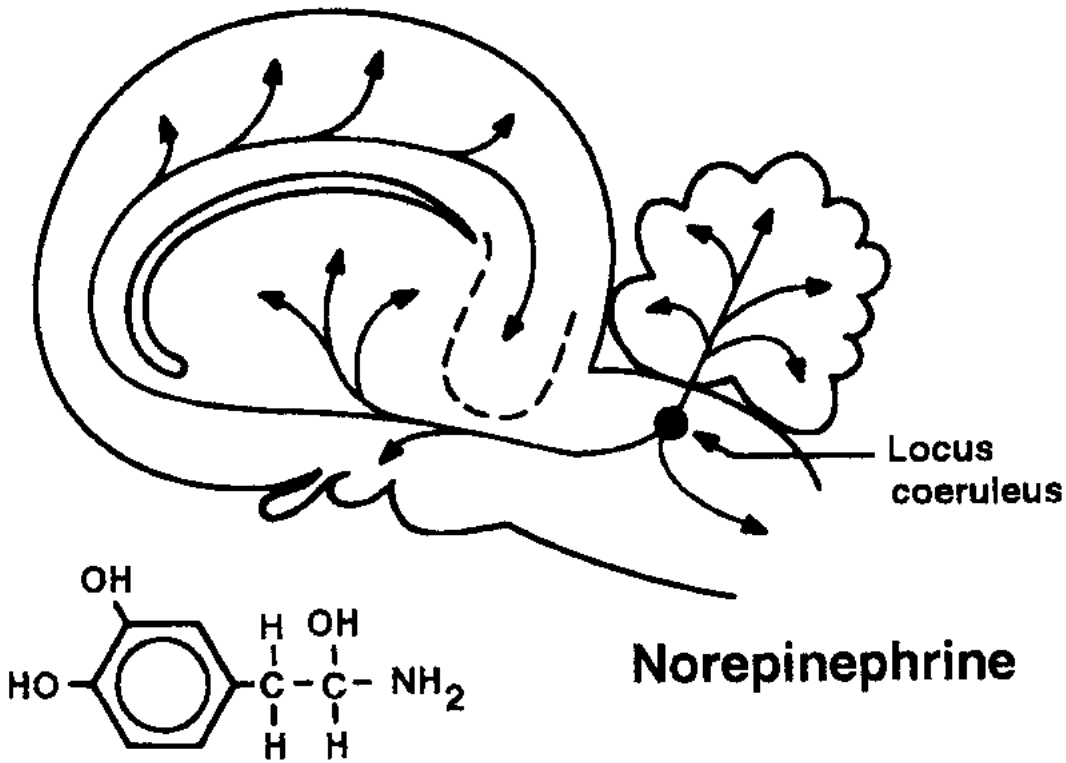


FIGURE 1-13. The primary projections of the noradrenergic locus coeruleus.

NOREPINEPHRINE

- *How is it made?*
  - See diagram
- *Rate limiting step in Production?*
  - Tyrosine Hydroxylase

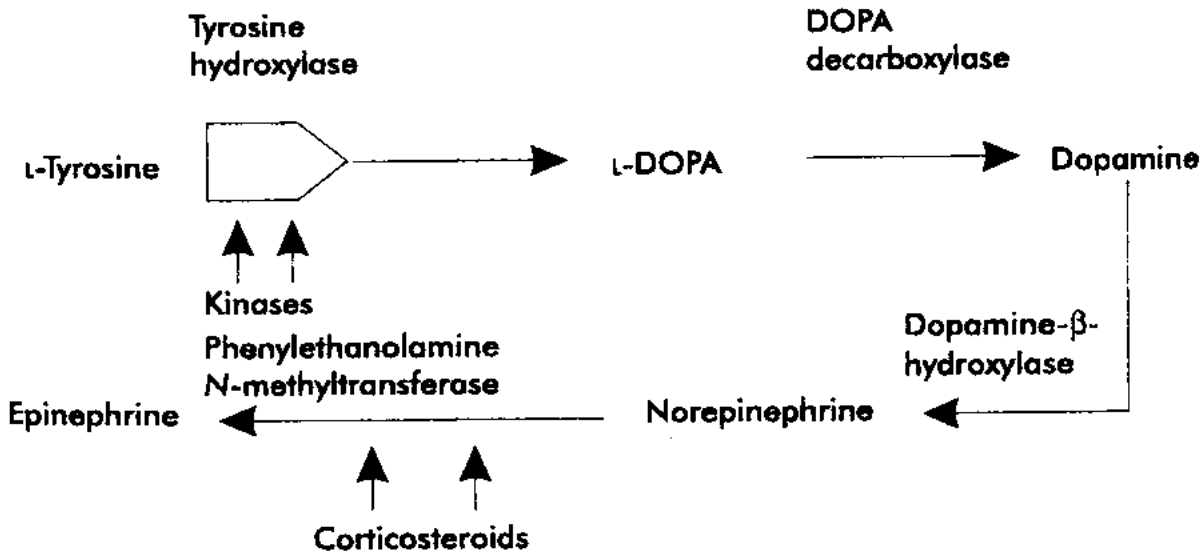


FIGURE 1–2. The biosynthetic pathway for catecholamines. Note that tyrosine hydroxylase is activated by phosphorylation by protein kinases, and the synthesis of phenylethanolamine-*N*-methyltransferase is regulated by corticosteroids.

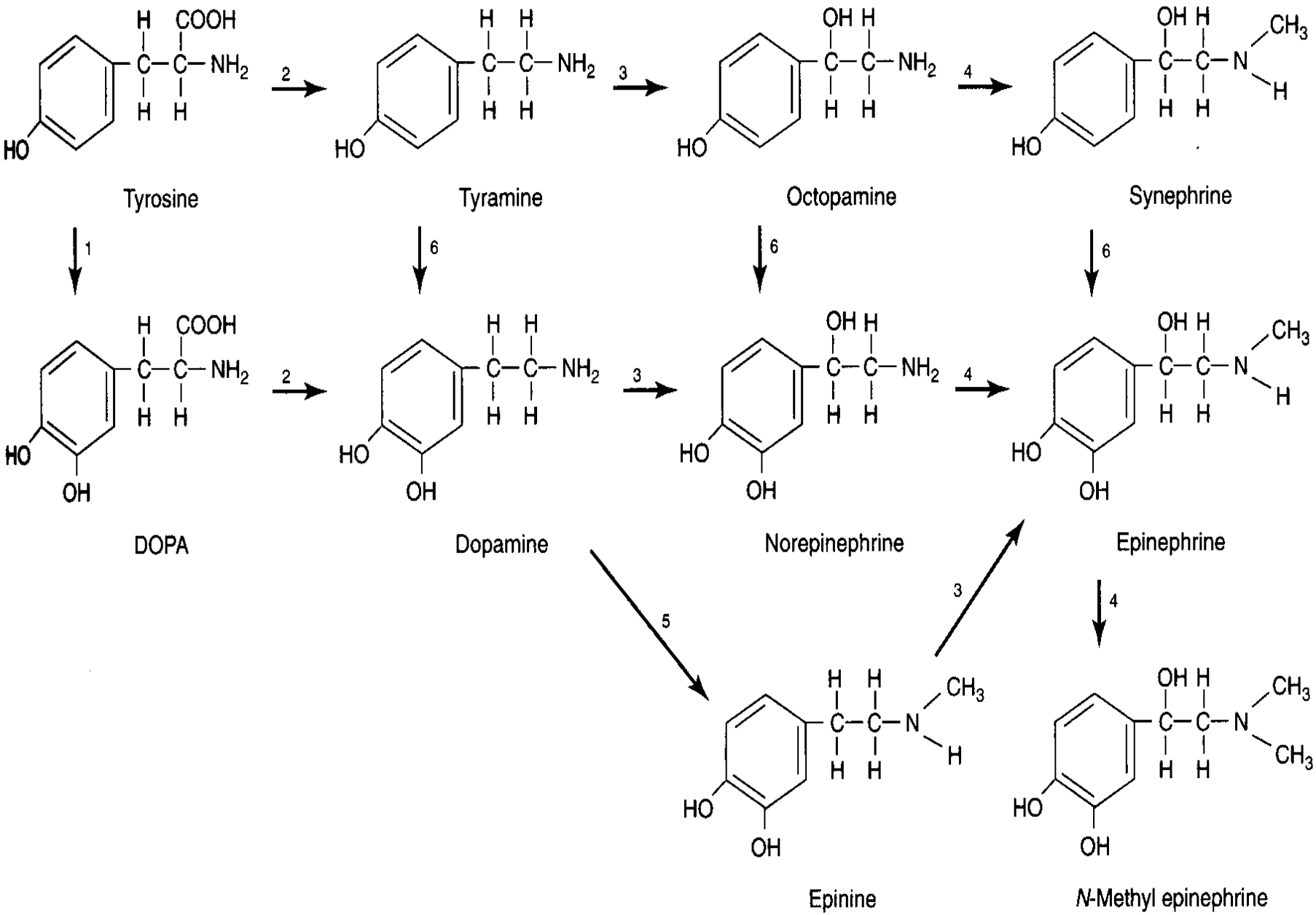

Tyrosine
Tyramine
Octopamine
Synephrine
DOPA
Dopamine
Norepinephrine
Epinephrine
Epinine
N-Methyl epinephrine
1
2
3
4
5
6

FIGURE 3.2–5

NOREPINEPHRINE

- *How is it metabolized?*
- Monoamine Oxidase (MAO)
    - mitochondria
- Catechol-O-Methyl Transferase (COMT)
    - synapse

NOREPINEPHRINE

- *Role?*
  - "Modulator" of CNS "tone"
  - Increases reactivity to sensory input

NOREPINEPHRINE

- *Clinical Significance?*
  - dysregulation may play a role in depressive and anxiety disorders
  - key component of the Stress Response

DOPAMINE

- *Where is it made?*
- Ventral Tegmental Area (mesolimbic/mesocortical tracts)
- Substantia Nigra (nigrastriatal tract)
- Arcuate Nucleus (to pituitary)

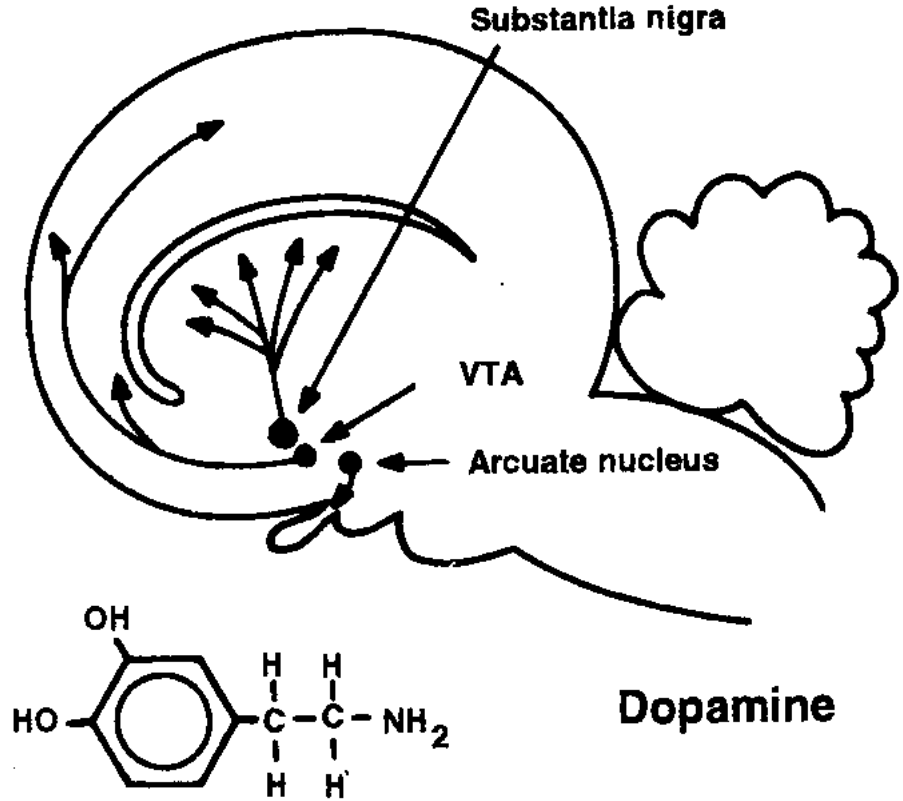
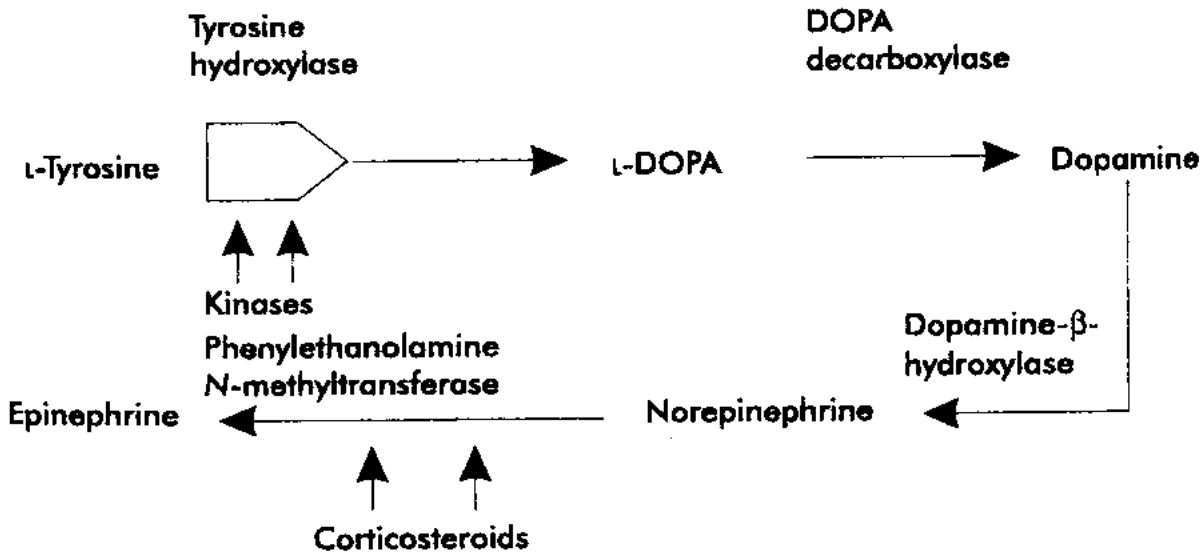


FIGURE 1–15. The three major dopaminergic pathways: the nigrostriatal pathway, the mesocorticolimbic pathway (originating in the ventral tegmental area [VTA]), and the arcuate nucleus pathway to the infundibulum.

DOPAMINE

- *How is it made?*
  - See diagram
- *Rate limiting step?*
- Tyrosine hydroxylase
- *How is it metabolized?*
- MAO
- COMT



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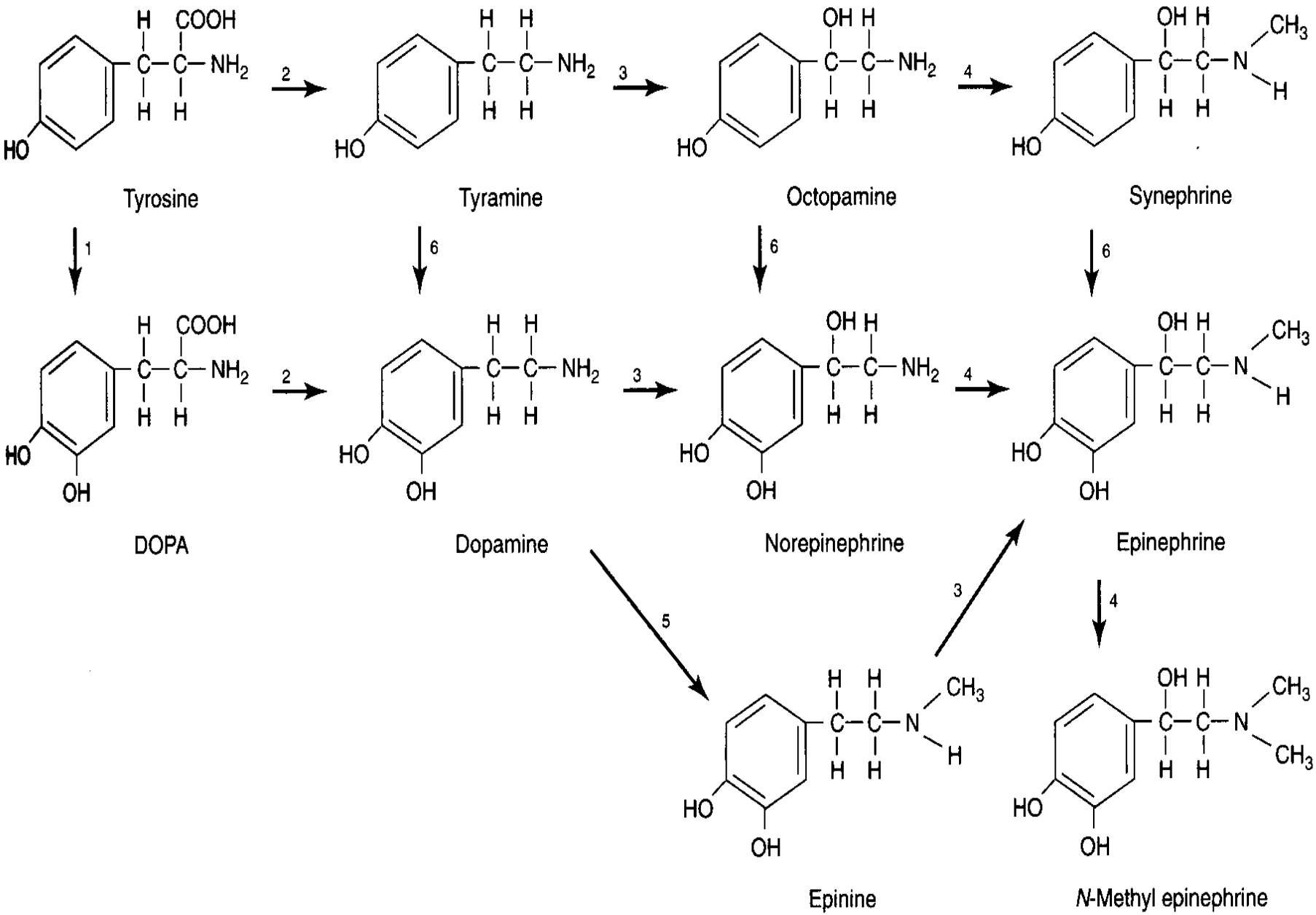

Tyrosine
Tyramine
Octopamine
Synephrine
DOPA
Dopamine
Norepinephrine
Epinephrine
Epinine
N-Methyl epinephrine
1
2
3
4
5
6

FIGURE 3.2–5

DOPAMINE

- *Role in the CNS?*
  - Mesolimbic tract - Reward, Pleasure
  - Mesocortical tract - Working memory, attention, motivation, cognitive integration
  - Pituitary - PIF
- *Clinical significance?*
  - Implicated in psychotic disorders and addictive disorders
  - Parkinsonism and other movement disorders

SEROTONIN

- *Where is it made?*
- Raphe nuclei in the Pons and Midbrain (projects throughout the brain)
- *Produced from?*
- From the amino acid Tryptophan
- *Rate limiting step?*
- Tryptophan Hydroxylase

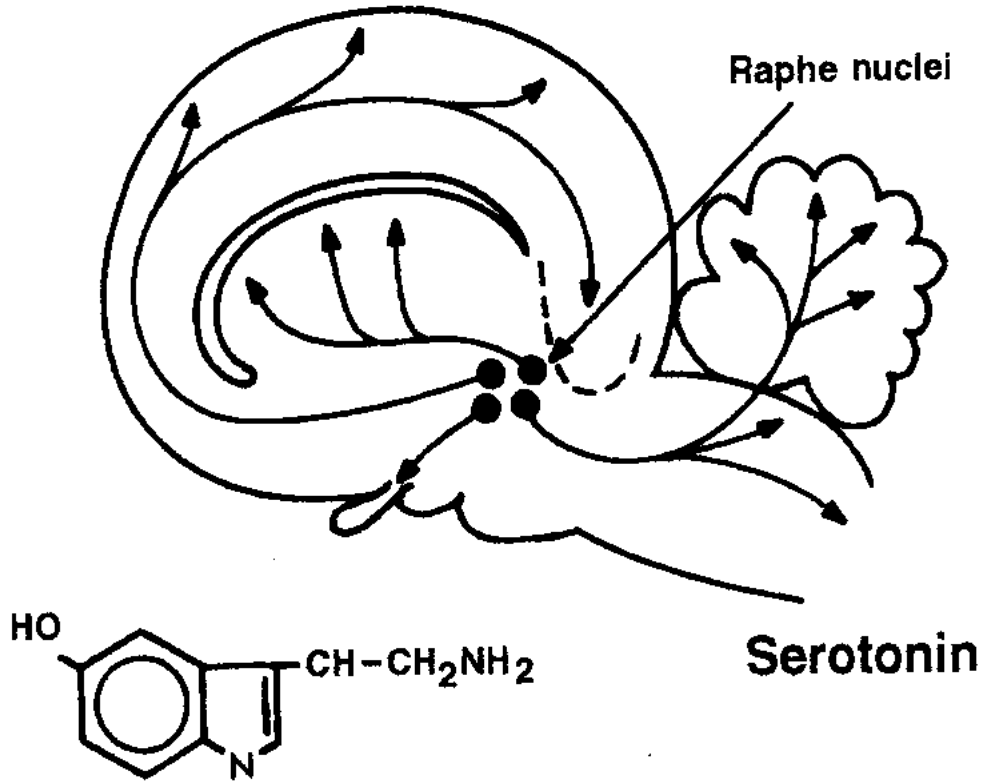
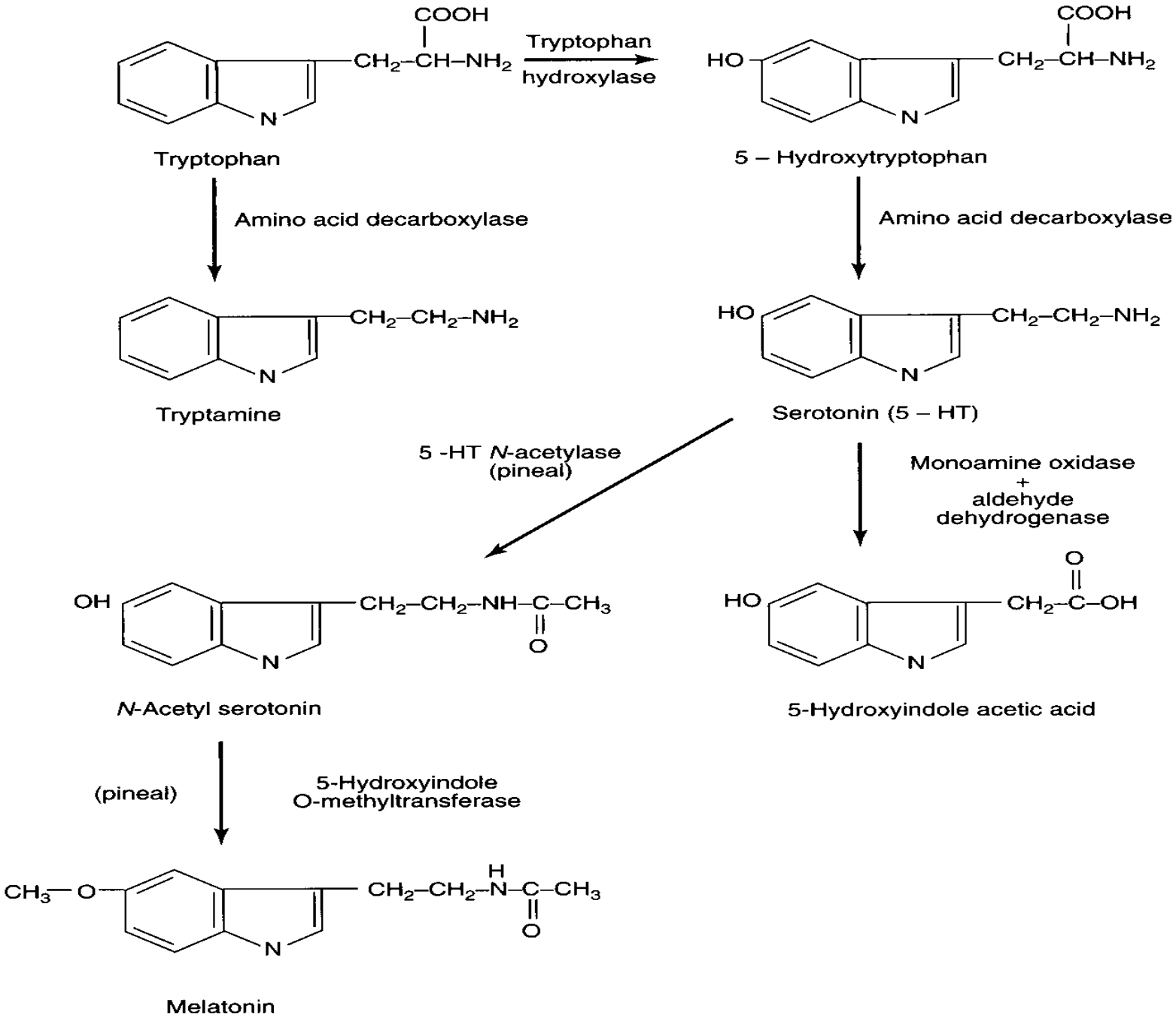


FIGURE 1–14. The pathways of the raphe serotonergic neurons.


COOH
CH2–CH–NH2
Tryptophan
hydroxylase
HO
Tryptophan
5 – Hydroxytryptophan
Amino acid decarboxylase
Amino acid decarboxylase
CH2–CH2–NH2
Tryptamine
Serotonin (5 – HT)
5 -HT N-acetylase
(pineal)
Monoamine oxidase
+
aldehyde
dehydrogenase
OH
CH2–CH2–NH–C–CH3
O
N-Acetyl serotonin
CH2–C–OH
5-Hydroxyindole acetic acid
(pineal)
5-Hydroxyindole
O-methyltransferase
CH3–O
H
CH2–CH2–N–C–CH3
Melatonin

SEROTONIN

- *Metabolism?*
  - MAO
  - COMT
- *Role?*
  - Modulator of neuronal tone in the CNS and sympathetic system
  - Plays a role in the regulation of sleep, temperature, pain, appetite, endocrine secretions, and mood.

SEROTONIN

- *Clinical Significance?*
  - Dysregulation implicated in the pathogenesis of: schizophrenia, personality disorders, obsessive-compulsive disorder, anxiety disorders, alcoholism, and chronic pain.

ACETYLCHOLINE

- *Where is it made?*
- Nucleus basalis of Meynert, diagonal band of Broca, and medial septal region (projects throughout the brain), there are also local cholinergic interneurons in the striatum
- *Role in the CNS?*
  - Attention, memory, learning, possibly mood and sleep

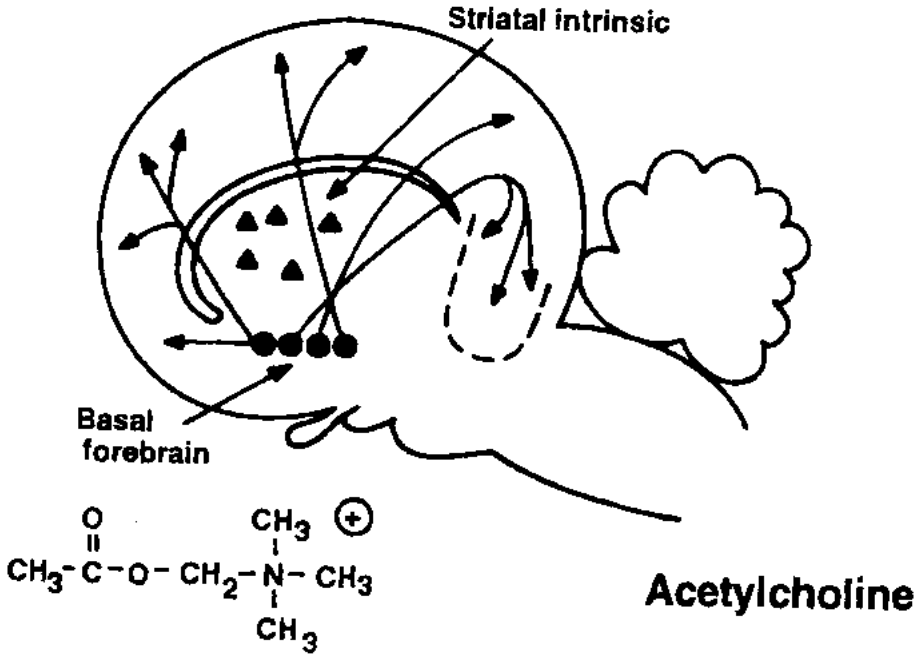


FIGURE 1-16. The forebrain cholinergic neurons. Cholinergic neurons in the basal forebrain, including the nucleus basalis of Meynert, the diagonal band of Broca, and the medial septal nucleus, innervate the cerebral cortex, hippocampus, and limbic structures. The striatum contains local circuit cholinergic interneurons.

ACETYLCHOLINE

- *Clinical significance?*
  - Cholinergic loss can lead to dementia or delirium

AMINO ACIDS

- GABA - major inhibitory neurotransmitter
- GLUTAMATE - major excitatory neurotransmitter
  - NMDA receptor
    - PCP
    - Learning via LTP
    - Excitotoxicity and neuronal damage

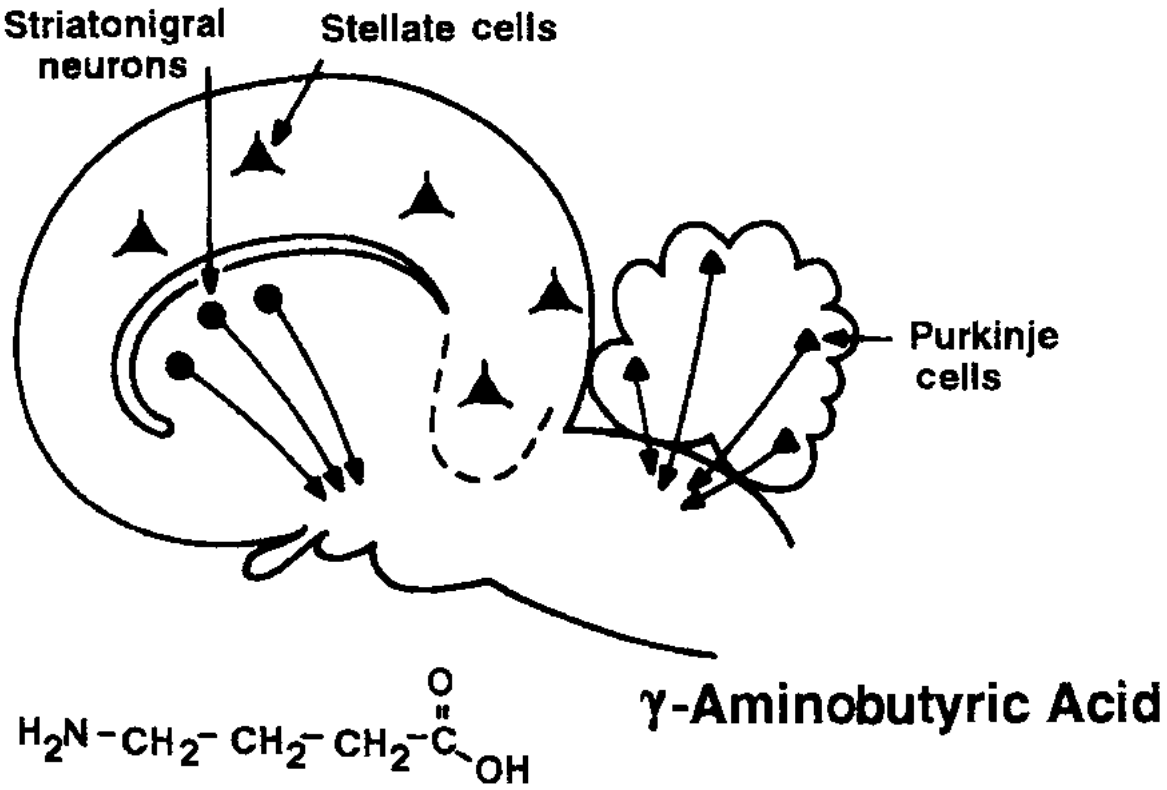


FIGURE 1-17. Major GABAergic pathways. The inhibitory neurotransmitter GABA is synthesized by local circuit stellate cells within the cerebral cortex, by the cerebellar Purkinje cells, and by striatonigral neurons.

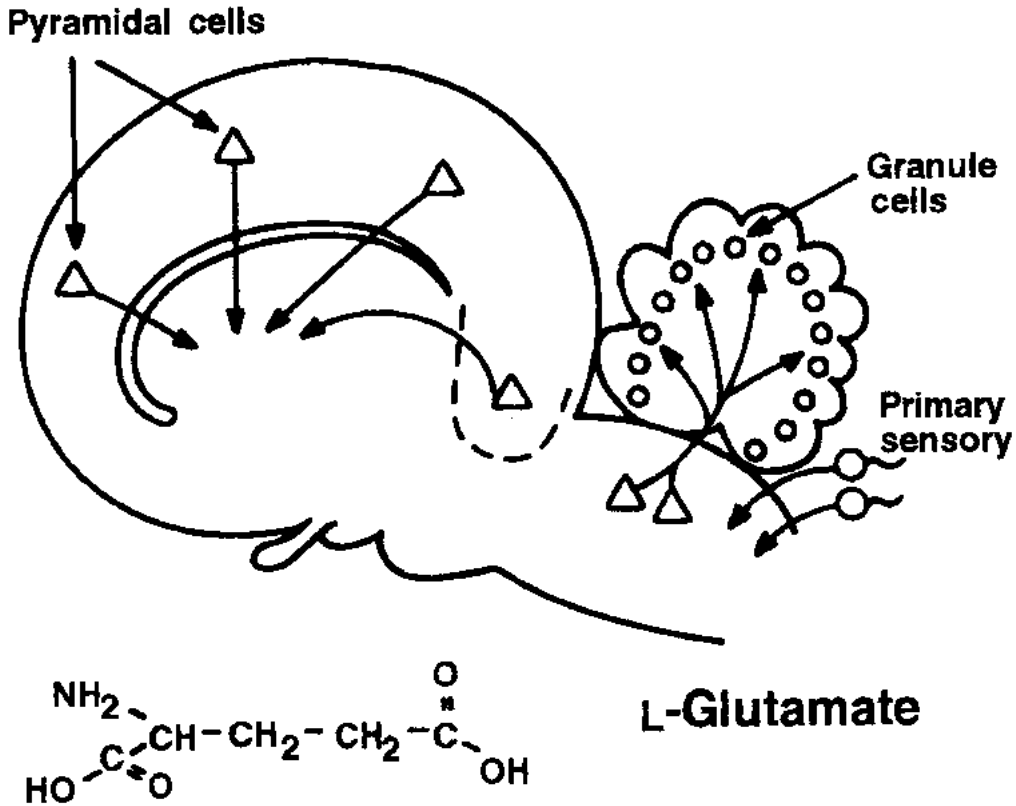


FIGURE 1-18. Major glutamatergic pathway. The excitatory neurotransmitter L-glutamic acid is released by a number of neurons including cortical and hippocampal pyramidal cells, cerebellar granule cells, cerebellar climbing fibers, and primary sensory afferents.